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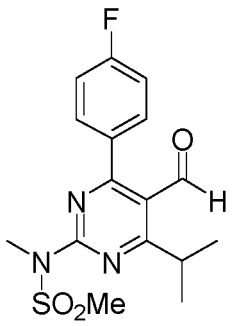
Description

[0001] The invention is directed to a process for preparing a rosuvastatin precursor. In particular, the invention is directed to a process for preparing N-(5-cyano-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-N-methylmethanesulfonamide and optionally subjecting this compound to a reduction step to form N-(4-(4-fluorophenyl)-5-formyl-6-isopropylpyrimidin-2-yl)-N-methylmethanesulfonamide.

[0002] Rosuvastatin, in particular rosuvastatin calcium, is a well-known HMG-CoA reductase inhibitor which is used for the treatment of hypercholesterolemia and to prevent cardiovascular disease. The compound according to formula (I):



(I)

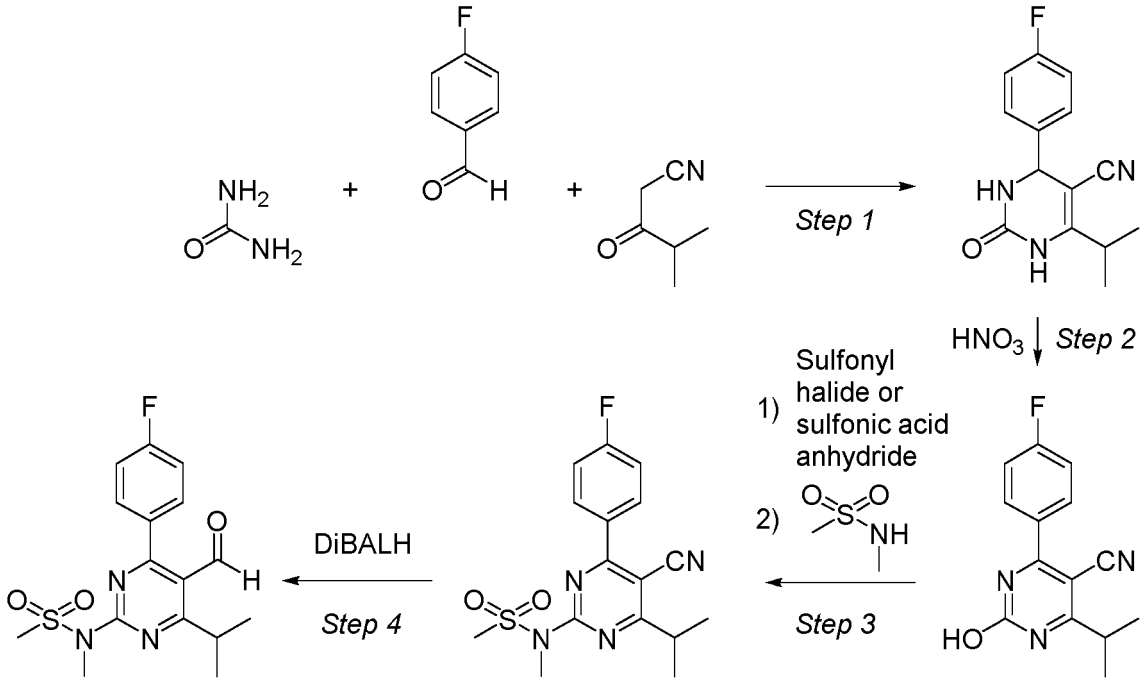
is a well-known precursor for preparing rosuvastatin. Different processes are known to prepare the compound of formula (I).

[0003] One such process is described in WO 2008/151510, wherein the compound of formula (I) is prepared from p-fluorobenzaldehyde, 4-methyl-3-oxopentanenitrile and urea. This process is represented in the reaction scheme below.

[0004] A disadvantage of the process of WO 2008/151510 is that each step is typically conducted in a separate solvent. Preferred solvents in the first step are methanol, ethanol and isopropanol. Preferred solvents in the second step are carboxylic acids, such as acetic acid, propionic acid and butyric acid. The most preferred solvents in the third step include ethyl acetate, butyl acetate and acetonitrile. Examples of solvents for the fourth step are benzene, toluene, xylene, dichloromethane, chloroform, tetrahydrofuran and dioxane. The use of different solvents in different reaction steps is generally not desirable in an industrial process, both in view of handling costs and recycling issues.

[0005] An object of the invention is to provide a process for preparing the compound of formula (I), wherein the same solvent is used in at least two subsequent steps.

[0006] In particular, it is an object of the invention to conduct the two reactions in step 3 and the reaction in step 4 of WO 2008/151510 in the same solvent. No solvent is described in WO2008/151510 that is considered suitable for each of the three reactions in step 3 and 4.



[0007] From an industrial perspective, it is highly desirable to use a single solvent for several process steps. In general for an efficient process, solvents need to be re-cycled in the process. Therefore handling of only one solvent is preferred to avoid several recovery plants. The use of toluene is highly preferred over, for example acetonitrile and n-butylacetate (which are suggested as preferred solvents for the third step in WO 2008/151510) due to the favourable azeotrope and low water solubility of toluene, which allows a very high recovery yield. Due to its miscibility with water, acetonitrile is far from preferred in this process as it would require an additional solvent for extraction and isolation.

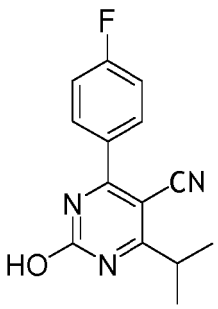
[0008] Surprisingly, it was found that this reaction can be effectively carried out in toluene as both a base, like for example potassium carbonate as well as the substrate are nearly insoluble in toluene. This in contrast to, for example acetonitrile, which is a highly polar solvent wherein substrate and the base have a significant higher polarity. It is not obvious to choose for toluene in this type of chemistry. In general, more polar solvents like DMSO or NMP would be chosen by a person skilled in the art.

[0009] Finally, a single solvent like toluene allows integration of several steps, avoiding isolation and therefore increasing the overall yield.

[0010] Thus, the inventors found that the object could be met by using toluene as the solvent. Although the starting compound in step 3 (herein also referred to as the hydroxy-pyrimidine-carbonitrile) showed a low solubility in toluene, thus resulting in the reaction mixture being a suspension, the inventors found that the presence of undissolved hydroxy-pyrimidine-carbonitrile did not hinder the reaction as much as would be expected. In fact, the reaction resulted in an acceptable yield.

[0011] Accordingly, the invention is directed to a process for preparing a rosuvastatin precursor, comprising the steps of:

(a) providing a starting mixture comprising the compound of formula (II)

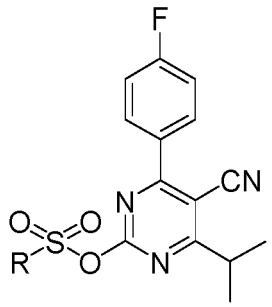


(II)

and toluene; and

(b) a first reaction step, wherein the starting mixture is contacted with an organic sulfonyl halide; and the resulting

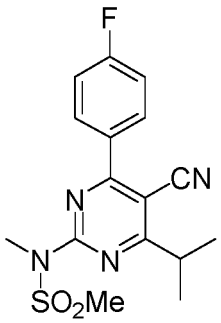
first reaction mixture is kept at a first temperature of below 110 °C, thereby forming an intermediate mixture comprising the compound of formula (III)



(III)

wherein R is an organic group; and

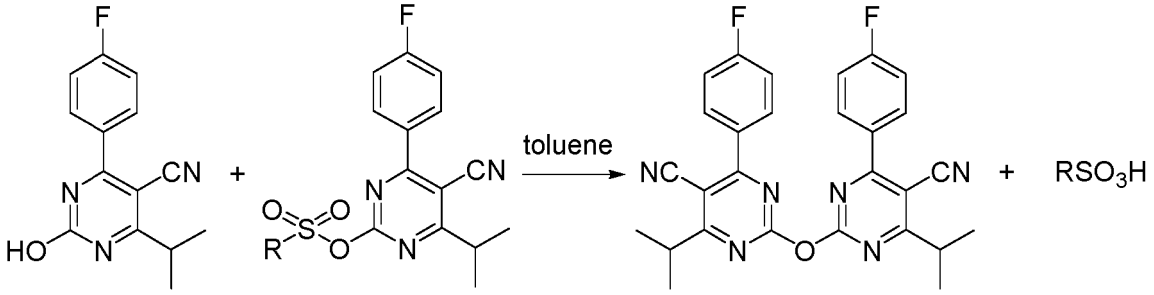
(c) a second reaction step, wherein the intermediate mixture is contacted with N-methylmethane sulfonamide; and the resulting second reaction mixture is kept at a second temperature, thereby forming a second mixture comprising the compound of formula (IV), wherein at least 95 wt.% of the solvent present in the starting mixture, the first reaction mixture, the intermediate mixture, and the second reaction mixture is toluene.



(IV)

[0012] The compound of formula (IV) obtained in the second reaction step may subsequently be subjected to a reduction step in toluene, typically using diisobutylaluminium hydride (DIBALH) as the reducing agent. It is advantageous that the reduction step uses the same solvent as the first and second reaction steps. Besides the advantages in solvent recycling, this also allows for the possibility of integrating such steps and/or skipping isolation steps of intermediates obtained in such steps, for example those obtained in the second reaction step.

[0013] The inventors further found that when performing the step of reacting the hydroxy-pyrimidine-carbonitrile with an organic sulfonyl halide (first reaction step) and subsequently with N-methylmethane sulfonamide (second reaction step) in toluene, these reaction steps resulted in the formation of a dimer. Without wishing to be bound by any theory, the inventors expect that the following side-reaction takes place:



[0014] The inventors realized that in order to obtain a good yield in toluene, formation of the dimer should be prevented, or at least reduced. They found that this could be achieved by conducting the reaction at relatively low temperatures, preferably below 110°C. Furthermore, they found that when using a specific dosing protocol for contacting the N-methylmethane sulfonamide with the intermediate mixture, the formation of the dimer could be prevented even further. According to this dosing protocol, the intermediate mixture is added to a mixture of N-methylmethane sulfonamide in

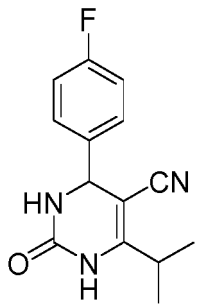
toluene over a period of time of at least one hour. These measures to reduce dimerization are discussed in more detail further below.

[0015] As used herein, the term "rosuvastatin precursor" will generally refer to the compound of formula (I). However, in case the process of the invention is conducted without the reduction step, the rosuvastatin precursor may also refer to the compound of formula (IV).

[0016] Unless noted otherwise, the term "mixture" as used herein typically refers to a solution (e.g. in case of the intermediate mixture and second reaction mixture). Exceptions are the starting mixture and the initial first reaction mixture, which are typically suspensions, as explicitly explained below. Furthermore, the term "mixture" as used herein typically refers to a mixture wherein the main solvent is toluene. This means that at least 95 wt.%, even more preferably at least 99 wt.%, even more preferably at least 99.9 wt.% of the solvent present in the mixture is toluene.

[0017] The process of the invention is discussed in detail herein below. The process of the invention is primarily directed to three reaction steps. In the first reaction step, the hydroxy-pyrimidine-carbonitrile of formula (II) is reacted with an organic sulfonyl halide to form the sulfonate-pyrimidine-carbonitrile of formula (III), generally in the presence of a base. In the second reaction step, the sulfonate-pyrimidine-carbonitrile is reacted with N-methylmethane sulfonamide to form the pyrimidinyl-sulfonamide of formula (IV). In the third step (reduction step), the pyrimidinyl-sulfonamide of formula (IV) is reacted with a reducing agent to obtain the rosuvastatin precursor of formula (I).

[0018] According to the process of the invention, first a starting mixture is provided comprising the compound of formula (II). This compound is typically prepared by reacting p-fluorobenzaldehyde, 4-methyl-3-oxopentanenitrile and urea to form the compound of formula (V)



(V)

and subsequently oxidizing this compound to form the compound of formula (II). These reactions may for example be conducted by following the process as described in WO2008/151510.

[0019] Since the compound of formula (II) has a low solubility in toluene, the compound of formula (II) is typically suspended in the toluene in the starting mixture. The starting mixture is thus typically in the form of a suspension. At least 95 wt.%, preferably at least 99 wt.%, even more preferably at least 99.9 wt.% of the organic solvent present in the starting mixture is toluene. Most preferably, toluene is the only solvent present in the starting mixture. The use of a single solvent is desirable in view of handling costs and recycling issues, as well as the integration with other reaction steps. The starting mixture may comprise 1-30 wt.%, for example 5-20 wt.% of the compound of formula (II), based on the total weight of toluene present in the mixture. The same weight percentages may also apply to the reaction mixture after having contacted the organic sulfonyl halide. Typically, no significant amount of toluene is added during contacting of this compound.

[0020] In the first reaction step, the compound of formula (II) is reacted with an organic sulfonyl halide to form the compound of formula (III). An organic sulfonyl halide is a compound of the general formula R-SO_2X, wherein X is a halide and R is an organic group, typically having 1 up to 15 carbon atoms. The halide may be chloride, bromide, fluoride or iodide. The organic group may be a substituted or unsubstituted aromatic hydrocarbon (preferably phenyl or naphthyl), alkane (preferably methyl, ethyl, propyl or butyl) or cycloalkane. In case the organic group is substituted, the organic group may be substituted with one or more substituting groups, which are preferably selected from C1-C4 alkyl (preferably methyl), halide (e.g. Cl, Br, F, I) and nitro (NO_2). The definition of the R group given above for the organic sulfonyl halide also applies to the R group of the compound of formula (III).

[0021] Examples of suitable organic sulfonyl halides are methanesulfonyl chloride, ethanesulfonyl chloride, trifluoromethanesulfonyl chloride, methanesulfonyl bromide, benzenesulfonyl chloride, benzenesulfonyl bromide, p-toluenesulfonyl chloride, p-toluenesulfonyl bromide, p-toluenesulfonyl fluoride, 4-chlorobenzenesulfonyl chloride, 2-chlorobenzenesulfonyl chloride, 2-nitrobenzenesulfonyl chloride, 2-naphtalenesulfonyl chloride and 2,4,6-trimethylbenzenesulfonyl chloride. Good results have been obtained using organic sulfonyl chlorides. Preferably, p-toluenesulfonyl chloride (p-TsCl) is used as the organic sulfonyl chloride.

[0022] The starting mixture comprising the compound of formula (II) is first contacted with the organic sulfonyl halide to form the reaction mixture. This can be done by adding the organic sulfonyl halide to the starting mixture, for example

during a period of time of 1-60 minutes.

[0023] The reaction mixture obtained after contacting is kept at a first temperature, thereby forming an intermediate mixture comprising the compound of formula (III). The first temperature is preferably a temperature of between 50 °C and 110 °C, more preferably between 60 °C and 100 °C, for example between 70 and 90 °C or between 75 and 85 °C. The reaction mixture may be kept at the first temperature for an appropriate duration, for example for at least 1 hour, preferably for at least 2 hours, for example at least 3 hours.

[0024] The reaction between the compound of formula (II) and the organic sulfonyl halide is typically conducted in the presence of a base. The base may for example be selected from the group consisting of potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, sodium methoxide, potassium methoxide, sodium tert-butoxide, potassium tert-butoxide, sodium tert amyl alcohol and potassium tert amyl alcohol. Good results have been achieved using an inorganic base. Preferably, the base is potassium carbonate. The molar amount of base used in the reaction may be at least equal, for example 1-5 times the molar amount of the compound of formula (II) present in the mixture. Preferably, the base is present in the starting mixture. Nevertheless, the base may also be contacted with the starting mixture, e.g. during or after contacting the starting mixture with the organic sulfonyl halide. This is typically achieved by simply adding the base to the starting mixture. Accordingly, the first reaction mixture will comprise the base.

[0025] After conducting the first reaction step, the resulting intermediate mixture is subjected to the second reaction step. Preferably, the compound of formula (III) is not isolated between the first and second reaction step. Rather, the compound of formula (III) is kept in solution in toluene in the intermediate mixture until it is reacted further in the second reaction step. Thus, the first and second reaction step may be conducted in the same reaction vessel.

[0026] In the second reaction step, the compound of formula (III) is reacted with N-methylmethane sulfonamide to form the compound of formula (IV).

[0027] The intermediate mixture comprising the compound of formula (III) is first contacted with N-methylmethane sulfonamide. The resulting reaction mixture (referred to as the 'second reaction mixture') is kept at a second temperature for an appropriate time to form a second mixture comprising the compound of formula (IV).

[0028] Contacting the intermediate mixture with N-methylmethane sulfonamide can be done by simply adding the N-methylmethane sulfonamide to the intermediate mixture, for example during a period of time of 1-180 minutes. To avoid the formation of dimers, the two reagents are preferably brought into contact with each other over a relatively long amount of time. For example, the N-methylmethane sulfonamide may be added (typically drop wise) to the intermediate mixture during a period of time of at least 1 hour, preferably at least 1.5 hours.

[0029] The inventors found that dimerization may in particular be avoided when using a specific dosing protocol, wherein the intermediate mixture is brought in contact with the N-methylmethane sulfonamide in a very specific manner. According to this dosing protocol, the intermediate mixture is added (typically drop wise) to a mixture comprising N-methylmethane sulfonamide, toluene and optionally a base (hereinafter referred to as the sulfonamide mixture). Contacting the reagents in this way was found to result in a significant reduction in dimer formation. The intermediate mixture is preferably added slowly, over a relatively long period of time, in order to reduce the occurrence of dimerization. Accordingly, the intermediate mixture is added to the sulfonamide mixture over a period of time of at least 0.5 hour, preferably at least 1 hour, more preferably at least 2 hours, even more preferably at least 2.5 hours. The sulfonamide mixture may comprise 1-60 wt.%, preferably 10-50 wt.% N-methylmethane sulfonamide, relative to the total weight of toluene in the sulfonamide mixture. The sulfonamide mixture may have a temperature of between 50°C and 110°C, preferably between 60°C and 100°C, for example between 70°C and 90°C or between 75°C and 85°C during contacting. The intermediate mixture may have a temperature in this same range. The base that may be present in the sulfonamide mixture is typically the same type of base that is typically present in the reaction between the compound of formula (III) and N-methylmethane sulfonamide. The molar amount of N-methylmethane sulfonamide present in the sulfonamide mixture may be at least 0.9 times, preferably 1.0 to 1.3 times the molar amount of the compound of formula (III) present in the intermediate mixture

[0030] The reaction mixture obtained after having contacted the different reagents is kept at a second temperature for an appropriate duration, preferably for at least 1 hour, more preferably at least 2 hours, for example at least 3 hours. The second temperature is preferably a temperature of between 50°C and 110°C, more preferably between 60°C and 100°C, for example between 70°C and 90°C or between 75°C and 85°C. Thus, a mixture is obtained comprising the compound of formula (IV), which mixture is herein referred to as the second mixture.

[0031] The reaction between the compound of formula (III) and N-methylmethane sulfonamide is typically conducted in the presence of a base. The base may for example be selected from the group consisting of potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, sodium methoxide, potassium methoxide, sodium tert-butoxide, potassium tert-butoxide, sodium tert amyl alcohol and potassium tert amyl alcohol. Good results have been obtained using an inorganic base. Preferably, the base is potassium carbonate. The molar amount of base used in the reaction may be at least equal, for example 1-5 times the molar amount of the compound of formula (III) present in the mixture. This base may be the same or a different base than the one already present in the first reaction step. The base may already be present in the intermediate mixture. Alternatively, or in addition, additional base may be added for the

second reaction step. In this case, the intermediate mixture may be contacted with additional base, either before, during or after contacting with the organic sulfonyl halide. The additional base may for example be contacted with the intermediate mixture by simply adding the base to the intermediate mixture. This is typically done before contacting the intermediate mixture with the N-methylmethane sulfonamide. In case of the specific dosing protocol described above, the base will preferably be present in the mixture of N-methylmethane sulfonamide and toluene.

[0032] After forming the compound of formula (IV) in the second reaction step, the second mixture may be washed with toluene and/or water.

[0033] The compound of formula (IV) may then be isolated, for example by concentrating the second mixture and subsequently crystallizing the compound of formula (IV), *e.g.* by cooling the reaction mixture. Alternatively, the compound of formula (IV) is kept in dissolved form in the (optionally washed) second mixture.

[0034] In the third step (also referred to as the reduction step), the compound of formula (IV) is reacted with a reducing agent to form the compound of formula (I). The reducing agent is preferably DIBALH. The inventors found that very good results could be obtained for the reduction in toluene using this specific reducing agent.

[0035] The inventors further found that a relatively small amount of DIBALH is already sufficient to obtain an efficient and complete reduction. The molar amount of DIBALH used in the reaction may be 1.0 to 1.5 times, preferably 1.1 to 1.3 times the molar amount of the compound of formula (IV). In other words, only 1.0 to 1.5 molar equivalents, preferably 1.1 to 1.3 equivalents of DIBALH are preferably used per equivalent of the compound of formula (IV) for the reduction.

[0036] The mixture of the compound of formula (IV) in toluene may comprise 5-50, preferably 10-40 wt.% of the compound of formula (IV), based on the total weight of toluene in the mixture. The mixture of the compound of formula (IV) in toluene may be the second mixture obtained in the second reaction step. Alternatively, in case the compound of formula (IV) was isolated from the second mixture, the mixture may instead be prepared from dissolving the compound of formula (IV) isolated in the second reaction step in toluene. Due to the low solubility of the compound of formula (IV) in toluene, the mixture may be a suspension.

[0037] The reduction reaction according to the process of the invention may be conducted by contacting a mixture of the compound of formula (IV) in toluene with a reducing agent, in particular with diisobutylaluminium hydride (DIBALH). DIBALH is preferably brought into contact with the mixture in the form of a solution in toluene. Good results were obtained using a DIBALH in toluene solution having a concentration of 10-40, preferably 20-30 wt.% DIBALH, based on the total weight of toluene in the solution.

[0038] The mixture of the compound of formula (IV) in toluene and the DIBALH solution in toluene are preferably brought into contact with each other at a temperature below 20°C, preferably a temperature of -50 to 10°C, more preferably of -20 to 0°C. This is typically done by adding the solution (typically drop wise) to the mixture over an amount of time of at least 15 minutes, preferably at least 0.5 hours.

[0039] After contacting, the reaction mixture is kept at a temperature below 20 °C, preferably a temperature of -50 to 10 °C, more preferably of -20 to 0 °C for an appropriate amount of time, typically 10-120 minutes. The resulting product mixture comprises the compound of formula (I).

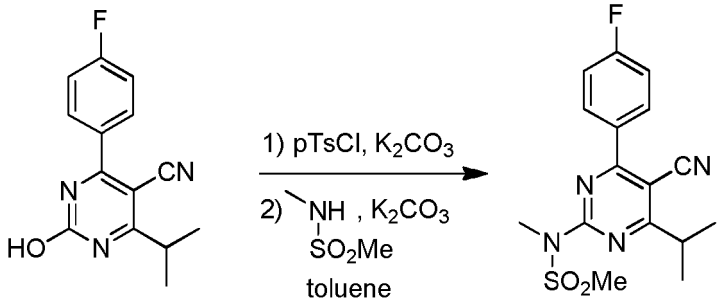
[0040] Subsequently, the product mixture may be quenched, for example by adding it to hydrochloric acid while keeping the temperature below 20 °C. The thus quenched product mixture is then heated to a temperature of 50-100 °C, after which the layers organic (toluene) layer may be separated from the aqueous layer. The compound of formula (I) may be isolated from the organic layer by concentration and crystallization, e.g. by cooling crystallization.

[0041] The invention is illustrated by the following experimental Examples.

EXAMPLES

Example 1A: Pyrimidine-Sulfonamide Formation in toluene

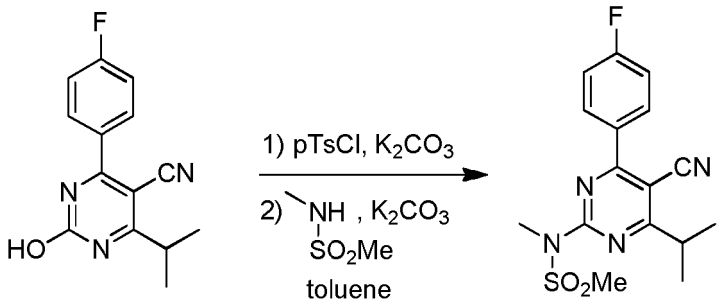
[0042] This Example shows the preparation of N-(5-cyano-4-(4-fluorophenyl)-6-isopropyl-pyrimidin-2-yl)-N-methyl-methanesulfonamide from 4-(4-fluorophenyl)-2-hydroxy-6-iso-propylpyrimidine-5-carbonitrile in toluene. The reaction mechanism is as follows.



[0043] A reactor is charged with toluene (90 mL), (4-fluorophenyl)-2-hydroxy-6-isopropyl pyrimidine-5-carbonitrile (10 g, 38.9 mmol) and K_2CO_3 (17.2 g, 124.4 mmol). Then pTsCl (9.6 g, 50.5 mmol, para-toluene sulfonylchloride) is added under stirring in 30 min. The reaction mixture is heated to 100°C and kept at this temperature for 3 h. After cooling to 80°C, NMSA (6.4 g, 58.3 mmol, N-methylmethane sulfonamide) is added, followed by stirring at 80°C for 7 h. The reaction mixture contains approximately 10% of dimer during this step. Toluene (140 mL) is added followed by careful addition of water (170 mL). The reaction mixture is heated to 90°C. After stirring for 30 min, the phases are separated. The organic layer is concentrated under reduced pressure until crystallization of the product starts. Then distillation is stopped and the slurry is heated to 100°C until a clear solution is obtained. If required a small amount of toluene is added. The reaction mixture is cooled in 6 h to 20°C and stirred for 16 h. The precipitated solid is isolated by filtration and washed with toluene (3 x 8 mL). After drying, N-(5-cyano-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-N-methylmethane sulfonamide is obtained as a white solid (9.5 g, yield 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 - 1.40 (d, 6H, *J* = 6.9 Hz), 3.40 - 3.43 (m, 1H), 3.53 (s, 3H), 3.55 - 3.65 (m, 1H), 3.64 (s, 3H), 7.21 - 7.27 (m, 2H), 8.08 - 8.13 (m, 2H).

Example 1B: Pyrimidine-Sulfonamide Formation using Dosing Protocol

[0044] This Example shows the preparation of N-(5-cyano-4-(4-fluorophenyl)-6-isopropyl-pyrimidin-2-yl)-N-methylmethanesulfonamide from 4-(4-fluorophenyl)-2-hydroxy-6-iso-propylpyrimidine-5-carbonitrile in toluene, wherein a specific dosing protocol is used for adding the N-methylmethane sulfonamide. The reaction mechanism is as follows.



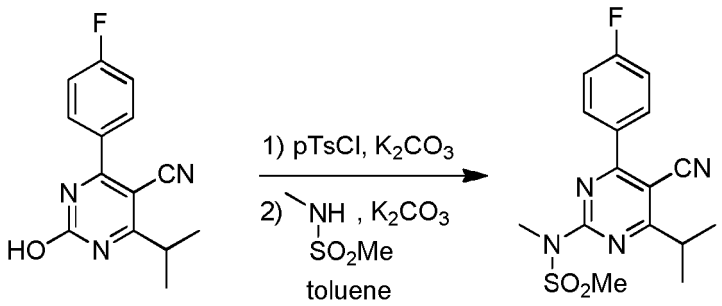
[0045] A reactor is charged with toluene (40 mL), 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl pyrimidine-5-carbonitrile (5.0 g, 19.4 mmol) and K_2CO_3 (4.0 g, 29.2 mmol). Then pTsCl (4.8 g, 25.3 mmol, para-toluene sulfonylchloride) is added under stirring in 15 min. The reaction mixture is heated to 100°C and kept at this temperature for 2 h, then cooled to 80°C (step A). In another reactor, a mixture of NMSA (3.2 g, 29.1 mmol N-methylmethane sulfonamide), K_2CO_3 (4.8 g, 33.1 mmol) in toluene (20 mL) was prepared and heated to 80°C (step B). The mass of step A is added 3 h at 80°C to the reaction mixture of step B. Thereafter, the total mass was stirred for another 4 h at 80°C. The reaction mixture contains approximately 5% of dimer during this step. The extraction and isolation procedure was done as described in example 4A to give N-(5-cyano-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-N-methylmethane sulfon amide as a white solid (5.3 g, yield 78%).

[0046] It can be concluded from Examples 4A and 4B that dimer formation can be reduced by using a dosing protocol. Only half the amount of dimers was formed in Example 4B (dosing protocol) compared to Example 4A (no dosing protocol). As a result, the yield of the pyrimidine-sulfonamide was increased from 70% in Example 4A to 78% in Example 4B.

Example 1C: Pyrimidine-Sulfonamide Isolation via Direct Filtration

[0047] This Example shows the preparation of N-(5-cyano-4-(4-fluorophenyl)-6-isopropyl-pyrimidin-2-yl)-N-methyl-

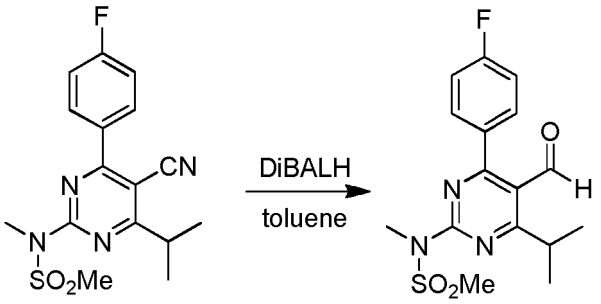
methanesulfonamide from 4-(4-fluorophenyl)-2-hydroxy-6-iso-propylpyrimidine-5-carbonitrile in toluene. The formed pyrimidine-sulfonamide was isolated directly from the reaction mixture using cooling filtration (as opposed to conducting an extraction step with water prior to filtration, as was done in Examples 1A and 1B). The reaction mechanism is as follows.



[0048] A reactor is charged with toluene (75 mL), (4-fluorophenyl)-2-hydroxy-6-isopropyl pyrimidine-5-carbonitrile (10 g, 38.9 mmol) and K_2CO_3 (6.4 g, 46.1 mmol). Then pTsCl is added (8.1 g, 42.5 mmol, para-toluenesulfonylchloride) under stirring in 30 min. The reaction mixture is heated to 110°C and kept at this temperature for 3 h. After cooling to 100°C, K_2CO_3 (7.4 g, 53.3 mmol) and NMSA (5.5 g, 50.4 mmol, N-methylmethane sulfonamide) are added. The reaction mixture is heated to 110°C, kept at this temperature for 3h, and then cooled to 20°C. The solids are isolated by filtration and washed with toluene (2 x 10 mL). This solid was suspended in water (50 mL) and stirred for 1 h at 20°C. The solid is isolated by filtration, washed with water (2 x 20 mL). After drying, N-(5-cyano-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-N-methylmethane sulfon amide is obtained as a white solid (9.5 g, yield 70%).

Example 2: Pyrimidine-Sulfonamide Reduction in toluene

[0049] This Example shows the preparation of N-(4-(4-fluorophenyl)-5-formyl-6-isopropyl-pyrimidin-2-yl)-N-methylmethanesulfonamide from N-(5-cyano-4-(4-fluorophenyl)-6-iso-propylpyrimidin-2-yl)-N-methylmethanesulfonamide using diisobutylaluminium hydride (DiBALH) as a reducing agent. The reaction mechanism is as follows.

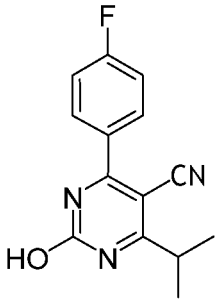


[0050] A reactor is charged with toluene (50 mL) and N-(5-cyano-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-N-methylmethanesulfonamide (6.0 g, 17.2 mmol) and cooled to -5°C. To the stirred white suspension is dosed in 1 h a solution of DiBALH in toluene (15.1 mL of a 25 w/w% solution of diisobutylaluminum hydride in toluene, 22.2 mmol) keeping the temperature at --5°C. Stirring is continued for 1 h at -5°C. Then this reaction mixture is added to 4M aqueous HCl (50 mL) keeping the temperature < 20°C. After the transfer is completed, toluene (10 mL) is used to transfer the last part of the reaction mixture into the aqueous HCl. The quenched reaction mixture is heated to 85°C. The layers are separated. The organic layer is concentrated under vacuum until precipitation occurs. Then distillation is stopped and the toluene is heated to 110°C. The clear solution is cooled in 5 h to 20°C and stirred for 16 h. The precipitated solid is isolated by filtration, washed with toluene (3 x 6 mL). After drying, N-(4-(4-fluorophenyl)-5-formyl-6-isopropylpyrimidin-2-yl)-N-methylmethanesulfonamide is obtained as a white solid (4.9 g, yield 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 - 1.34 (d, 6H, *J* = 7.0 Hz), 3.55 (s, 3H), 3.64 (s, 3H), 3.97 - 4.06 (m, 1H), 7.20 - 7.27 (m, 2H), 7.61 - 7.66 (m, 2H), 9.90 (s, 1H).

Claims

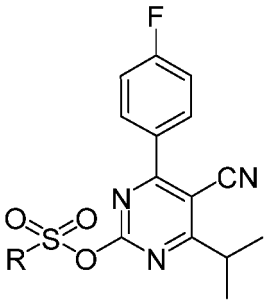
1. A process for preparing a statin precursor, comprising the steps of

(a) providing a starting mixture comprising the compound of formula (II) and toluene



(II)

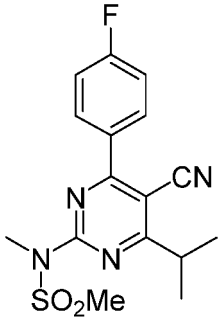
(b) a first reaction step, wherein the starting mixture is contacted with an organic sulfonyl halide; and the resulting first reaction mixture is kept at a first temperature of below 110 °C, thereby forming an intermediate mixture comprising the compound of formula (III)



(III)

wherein R is an organic group; and

(c) a second reaction step, wherein the intermediate mixture is contacted with N-methylmethane sulfonamide; and the resulting second reaction mixture is kept at a second temperature, thereby forming a second mixture comprising the compound of formula (IV)

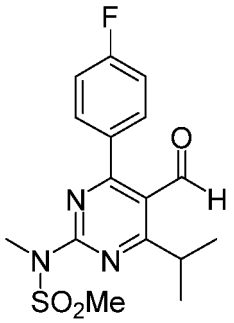


(IV)

,

wherein at least 95 wt.% of the solvent present in the starting mixture, the first reaction mixture, the intermediate mixture, and the second reaction mixture is toluene.

2. The process according to claim 1, further comprising a reduction step, wherein the compound of formula (IV) obtained in the second reaction step is reacted with a reducing agent in toluene to form the compound of formula (I).



(I)

3. The process according to any of the previous claims, wherein the first and second temperature are independently chosen to lie in the range of 50 to 110°C.

4. The process according to any of the previous claims, wherein the intermediate mixture is contacted with N-methylmethane sulfonamide by adding the intermediate mixture to a sulfonamide mixture comprising N-methylmethane sulfonamide in toluene.

5. The process according to claim 4, wherein the intermediate mixture is added to the mixture comprising N-methylmethane sulfonamide over a period of at least 1 hour.

6. The process according to claim 4 or 5, wherein the mixture comprising N-methylmethane sulfonamide further comprises a base.

7. The process according to any of claims 4-6, wherein the sulfonamide mixture comprises 1-60 wt.% N-methylmethane sulfonamide, relative to the total weight of toluene in the sulfonamide mixture.

8. The process according to any of the previous claims, wherein the organic sulfonyl halide is selected from the group consisting of methanesulfonyl chloride, ethanesulfonyl chloride, trifluoromethanesulfonyl chloride, methanesulfonyl bromide, benzenesulfonyl chloride, benzenesulfonyl bromide, p-toluenesulfonyl chloride, p-toluenesulfonyl bromide, p-toluenesulfonyl fluoride, 4-chlorobenzenesulfonyl chloride, 2-chlorobenzenesulfonyl chloride, 2-nitrobenzenesulfonyl chloride, 2-naphtalenesulfonyl chloride and 2,4,6-trimethylbenzenesulfonyl chloride.

9. The process according to any of the previous claims, wherein the first and second reaction are conducted in the presence of a base selected from the group consisting of potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, sodium methoxide, potassium methoxide, sodium tert-butoxide, potassium tert-butoxide, sodium tert-amyl alcohol and potassium tert-amyl alcohol.

10. The process according to any of the previous claims, wherein R is an aromatic hydrocarbon, alkane or cycloalkane, optionally substituted with one or more of C1-C4 alkyl, halide or nitro.

11. The process according to any of the previous claims, wherein the starting mixture is a suspension of the compound of formula (II) in toluene.

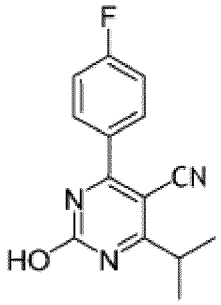
12. The process according to any of claims 2 -11, wherein the reducing agent is diisobutylaluminium hydride.

13. The process according to claim 12, wherein the reduction reaction is conducted by contacting a mixture of the compound of formula (IV) in toluene with a solution of DIBALH in toluene at a temperature below 20°C and keeping the resulting mixture at said temperature below 20 °C for an appropriate amount of time.

Patentansprüche

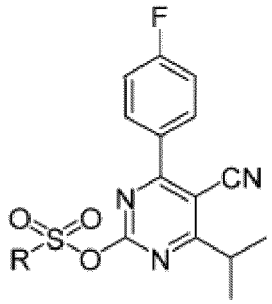
1. Verfahren zum Herstellen eines Statinvorläufers, umfassend die Schritte von:

(a) Bereitstellen eines Ausgangsgemischs, umfassend die Verbindung der Formel (II) und Toluol,



(II)

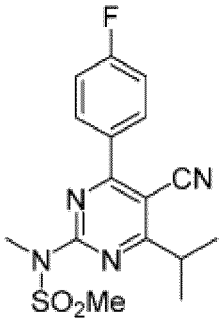
(b) einen ersten Reaktionsschritt, wobei das Ausgangsgemisch mit einem organischen Sulfonylhalogenid in Kontakt gebracht wird; und das resultierende erste Reaktionsgemisch bei einer ersten Temperatur von unter 110 °C gehalten wird, dadurch Bilden eines Zwischengemischs, umfassend die Verbindung der Formel (III),



(III)

wobei R eine organische Gruppe ist; und

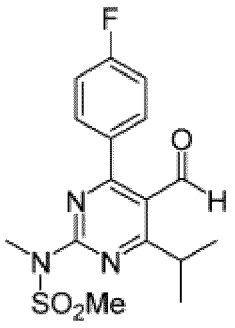
(c) einen zweiten Reaktionsschritt, wobei das Zwischengemisch mit N-Methylmethansulfonamid in Kontakt gebracht wird; und das resultierende zweite Reaktionsgemisch bei einer zweiten Temperatur gehalten wird, dadurch Bilden eines zweiten Gemischs, umfassend die Verbindung der Formel (IV),



(IV)

wobei mindestens 95 Gew.-% des Lösungsmittels, anwesend in dem Ausgangsgemisch, dem ersten Reaktionsgemisch, dem Zwischengemisch, und dem zweiten Reaktionsgemisch, Toluol ist.

2. Verfahren nach Anspruch 1, ferner umfassend einen Reduktionsschritt, wobei die Verbindung von Formel (IV), erhalten in dem zweiten Reaktionsschritt, mit einem Reduktionsmittel in Toluol reagiert wird, um die Verbindung der Formel (I) zu bilden,



(I)

3. Verfahren nach einem der vorhergehenden Ansprüche, wobei die erste und die zweite Temperatur unabhängig gewählt werden, um in dem Bereich von 50 bis 110 °C zu liegen.

4. Verfahren nach einem der vorhergehenden Ansprüche, wobei das Zwischengemisch mit N-Methylmethansulfonamid durch Zugeben des Zwischengemischs zu einem Sulfonamidgemisch, umfassend N-Methylmethansulfonamid in Toluol, in Kontakt gebracht wird.

5. Verfahren nach Anspruch 4, wobei das Zwischengemisch dem Gemisch, umfassend N-Methylmethansulfonamid, über einen Zeitraum von mindestens 1 Stunde zugegeben wird.

6. Verfahren nach Anspruch 4 oder 5, wobei das Gemisch, umfassend N-Methylmethansulfonamid, weiterhin eine Base umfasst.

7. Verfahren nach einem der Ansprüche 4 - 6, wobei das Sulfonamidgemisch 1-60 Gew.-% N-Methylmethansulfonamid umfasst, relativ zu dem Gesamtgewicht von Toluol in dem Sulfonamidgemisch.

8. Verfahren nach einem der vorhergehenden Ansprüche, wobei das organische Sulfonylhalogenid ausgewählt ist aus der Gruppe bestehend aus Methansulfonylchlorid, Ethansulfonylchlorid, Trifluormethansulfonylchlorid, Methansulfonylbromid, Benzolsulfonylchlorid, Benzolsulfonylbromid, p-Toluolsulfonylchlorid, p-Toluolsulfonylbromid, p-Toluolsulfonylfluorid, 4-Chlorbenzolsulfonylchlorid, 2-Chlorbenzolsulfonylchlorid, 2-Nitrobenzolsulfonylchlorid, 2-Naphthalinsulfonylchlorid und 2,4,6-Trimethylbenzolsulfonylchlorid.

9. Verfahren nach einem der vorhergehenden Ansprüche, wobei die erste und die zweite Reaktion in der Gegenwart einer Base durchgeführt werden, ausgewählt aus der Gruppe bestehend aus Kaliumcarbonat, Natriumcarbonat, Natriumhydroxid, Kaliumhydroxid, Natriummethoxid, Kaliummethoxid, Natrium-tert-butoxid, Kalium-tert-butoxid, Natrium-tert-amylalkohol und Kalium-tert-amylalkohol.

10. Verfahren nach einem der vorhergehenden Ansprüche, wobei R ein aromatischer Kohlenwasserstoff, Alkan oder Cycloalkan ist, optional substituiert mit einem oder mehreren von C1-C4-Alkyl, Halogenid oder Nitro.

11. Verfahren nach einem der vorhergehenden Ansprüche, wobei das Ausgangsgemisch eine Suspension der Verbindung von Formel (II) in Toluol ist.

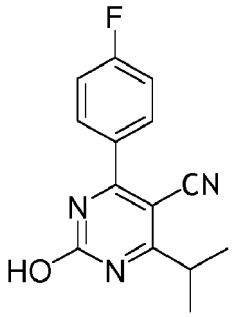
12. Verfahren nach einem der Ansprüche 2 - 11, wobei das Reduktionsmittel Diisobutylaluminiumhydrid ist.

13. Verfahren nach Anspruch 12, wobei die Reduktionsreaktion durch Inkontaktbringen eines Gemischs der Verbindung von Formel (IV) in Toluol mit einer Lösung von DIBALH in Toluol bei einer Temperatur unter 20 °C und Halten des resultierenden Gemischs bei der Temperatur unter 20 °C für eine angemessene Zeitdauer durchgeführt wird.

Revendications

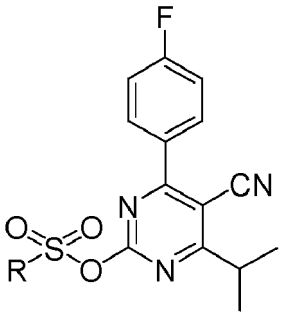
1. Procédé pour préparer un précurseur de statine, comprenant les étapes suivantes :

(a) fourniture d'un mélange de départ comprenant le composé de formule (II) et du toluène



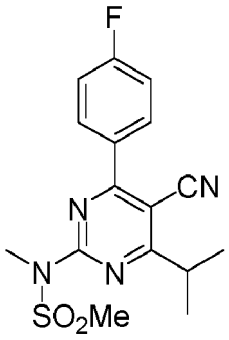
(II)

(b) une première étape de réaction, dans laquelle le mélange de départ est mis en contact avec un halogénure de sulfonyle organique ; et le premier mélange réactionnel résultant est maintenu à une première température inférieure à 110°C, en formant ainsi un mélange intermédiaire comprenant le composé de formule (III)



(III)

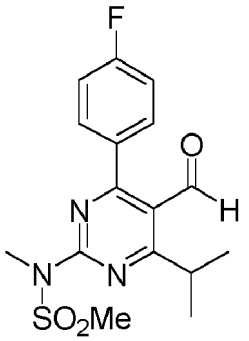
dans laquelle R est un groupe organique ; et
(c) une deuxième étape de réaction, dans laquelle le mélange intermédiaire est mis en contact avec du N-méthylméthanesulfonamide ; et le deuxième mélange réactionnel résultant est maintenu à une deuxième température, en formant ainsi un deuxième mélange comprenant le composé de formule (IV)



(IV)

dans lequel au moins 95 % en poids du solvant présent dans le mélange de départ, le premier mélange réactionnel, le mélange intermédiaire, et le deuxième mélange réactionnel consistent en du toluène.

2. Procédé selon la revendication 1, comprenant en outre une étape de réduction dans laquelle le composé de formule (IV) obtenu dans la deuxième étape de réaction est mis à réagir avec un agent réducteur dans du toluène pour former le composé de formule (I)



(I)

3. Procédé selon l'une quelconque des revendications précédentes, dans lequel les première et deuxième températures sont indépendamment choisies pour être situées dans la plage allant de 50 à 110 °C.

4. Procédé selon l'une quelconque des revendications précédentes, dans lequel le mélange intermédiaire est mis en contact avec du N-méthylméthanesulfonamide par addition du mélange intermédiaire à un mélange de sulfonamide comprenant du N-méthylméthanesulfonamide dans du toluène.

5. Procédé selon la revendication 4, dans lequel le mélange intermédiaire est ajouté au mélange comprenant du N-méthylméthanesulfonamide sur une période d'au moins 1 heure.

6. Procédé selon la revendication 4 ou 5, dans lequel le mélange comprenant du N-méthylméthanesulfonamide comprend en outre une base.

7. Procédé selon l'une quelconque des revendications 4 à 6, dans lequel le mélange de sulfonamide comprend 1 à 60 % en poids de N-méthylméthanesulfonamide par rapport au poids total du toluène dans le mélange de sulfonamide.

8. Procédé selon l'une quelconque des revendications précédentes, dans lequel l'halogénure de sulfonyle organique est choisi dans l'ensemble constitué par le chlorure de méthanesulfonyle, le chlorure d'éthanesulfonyle, le chlorure de trifluorométhanesulfonyle, le bromure de méthanesulfonyle, le chlorure de benzènesulfonyle, le bromure de benzènesulfonyle, le chlorure de p-toluènesulfonyle, le bromure de p-toluènesulfonyle, le fluorure de p-toluènesulfonyle, le chlorure de 4-chlorobenzènesulfonyle, le chlorure de 2-chlorobenzènesulfonyle, le chlorure de 2-nitrobenzènesulfonyle, le chlorure de 2-naphtalènesulfonyle et le chlorure de 2,4,6-triméthylbenzènesulfonyle.

9. Procédé selon l'une quelconque des revendications précédentes, dans lequel les première et deuxième réactions sont réalisées en présence d'une base choisie dans l'ensemble constitué par le carbonate de potassium, le carbonate de sodium, l'hydroxyde de sodium, l'hydroxyde de potassium, le méthylate de sodium, le méthylate de potassium, le tert-butylate de sodium, le tert-butylate de potassium, l'alcool tert-amylique sodique et l'alcool tert-amylique potassique.

10. Procédé selon l'une quelconque des revendications précédentes, dans lequel R est un hydrocarbure aromatique, alcane ou cycloalcane, éventuellement substitué par un ou plusieurs alkyles en C_1 à C_4, halogénures et nitro.

11. Procédé selon l'une quelconque des revendications précédentes, dans lequel le mélange de départ est une suspension du composé de formule (II) dans du toluène.

12. Procédé selon l'une quelconque des revendications 2 à 11, dans lequel l'agent réducteur est l'hydrure de diisobutylaluminium.

13. Procédé selon la revendication 12, dans lequel la réaction de réduction est réalisée par mise en contact d'un mélange du composé de formule (IV) dans du toluène avec une solution de DIBALH dans du toluène à une température inférieure à 20 °C et maintien du mélange résultant à ladite température inférieure à 20 °C pendant une quantité de temps appropriée.

REFERENCES CITED IN THE DESCRIPTION

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